REMARKS

The Office Action of April 5, 2004 has been carefully considered and the following response prepared. Claim 1-13 have been canceled without prejudice and replaced with new claims 18-40. Support for new claims 18-40 can be found in claims 1-13 as originally filed and throughout the specification, in particular at page 9, lines 23-32, page 10, lines 1-2, page 6, lines 11-21 and page 8. Claims 14-17 have been amended. No new matter has been added.

At page 2 of the Office Action, claims 1-13 were rejected under 35 USC 101. The Examiner indicated that claims 1-13 do not sufficiently distinguish over nucleic acids, proteins, cells and antibodies as they exist naturally. The Examiner suggested the claims be amended to indicate the hand of the inventor by the insertion of a phrase such as "transformed microorganism" or recombinant microorganism".

Applicants traverse this rejection. Claims 1-13 have been canceled and replaced with new claims 18-40. New claims 18-40 recite the step of culturing a transformed microorganism (claims 18-37) or a microorganism in which the activity of ilvD is increased as a result of mutation of the endogenous gene encoding ilvD (claims 30-40). Withdrawal of this section 101 rejection is requested.

At page 2 of the Office Action, the Examiner rejected claims 1-17 under 35 USC 112, first paragraph as not providing an adequate written description of the invention. The Examiner indicated that there was insufficient written description with respect to the microorganism used in the claimed methods and the enzymatic activities of dihydroxy acid dehydratase (ilvD), acetohydroxy acid synthase (ilvBN) or isomeroreductase (ilvC) that are "reinforced", increased, or "intensified", or enzymatic activities of threonine dehydratase (ilvA), ketopantoate hydroxymethyl transferase (panB) or pantothenate ligase (panC) that are "weakened or eliminated".

Applicants traverse this rejection. Claims 1-13 have been canceled without prejudice and replaced with new claims 18-40. New independent claims 18 and 38 state that the microorganism can produce L-valine from glucose, sucrose, lactose, fructose, maltose, molasses, starch, or cellulose or from glycerin or ethanol. The specification at

page 6 discloses that such microorganisms can be used in the methods of the invention. The terms "reinforced", increased and "intensified" have been removed from the claims and this rejection is now moot with respect to these terms.

With regard to "weakened or eliminated" activity, new claims 20, 33 and 34 state that the activity of ilvA in the microorganism is reduced or eliminated as a result of deletion of all or a part of the nucleotide sequence encoding said ilvA in the microorganism. Reduction or elimination of the activity of ilvA is disclosed in the specification at pages 8 and 9, and elimination of the activity of ilvA as a result of deletion of part of the nucleotide sequence encoding ilvA is shown in the specification in Example 2. Similarly, new claims 21, 24, and 35 state that the activity of at least one enzyme in the microorganism selected from the group consisting of panB, panC, panE and panD is reduced or eliminated as a result of deletion of all or a part of the nucleotide sequence encoding said enzyme in the microorganism. Reduction or elimination of the activity of panB, panC, panE and panD is disclosed at pages 9 and 10 of the specification and the elimination of panB and panC activity as a result of the deletion of the nucleotide sequences encoding these enzymes in the microorganism is shown in the specification in Example 4.

Applicants have provided sufficient written description of the invention. Withdrawal of this section 112, first paragraph rejection is requested.

At page 3, of the Office Action, the Examiner rejected claims 1-13 under 35 USC 112, second paragraph as being incomplete for omitting essential steps such as transforming the microorganism, culturing the microorganism in the appropriate medium containing substrates for production of L-valine, and isolating the produced L-valine.

Applicants traverse this rejection. Claims 1-13 have been canceled and replaced with new claims 18-40. Independent claims 18 and 30 recite the step of culturing a microorganism under conditions whereby L-valine is produced. Conditions for producing L-valine are disclosed in the specification at pages 10 and 11 and in the Examples. The methods of the invention as presently presented do not omit essential steps. It is not necessary that the L-valine produced by the methods of the invention be removed from the cell culture medium. In some embodiments of the invention, the microorganisms are transformed with nucleotide sequences encoding ilvD and/or

ilvBNC, whereas in other embodiments the endogenous ilvD gene and/or the ilvBNC genes are mutated. A separate step of transforming the microorganism is not essential, and, indeed, is not present in certain embodiments of the invention. Withdrawal of this section 112, second paragraph rejection is requested.

At page 4 of the Office Action, the Examiner rejected claims 1-17 under 35 USC 112, second paragraph as being indefinite. This rejection contained a number of separate rejections which will be answered separately.

Claims 1-3 were rejected as indefinite because of the phrase "gene expression are reinforced in a microorganism". This rejection is now moot in view of the cancellation of claims 1-3, and this phrase does not appear in any of the new claims added by this response.

Claims 4-13 were rejected as indefinite because of the phrase "characterized in that". This rejection is now moot in view of the cancellation of claims 4-13, and this phrase does not appear in any of the new claims added by this response.

Claim 5 was rejected as indefinite because of the phrase "mutation of the endogenous ilvD gene and/or of the ilvBNC genes serves to generate corresponding enzymes having increase activity". This rejection is now moot in view of the cancellation of claim 5.

Claim 6 was rejected as indefinite because of the phrase "gene expression are intensified by increasing the number of genocopies". This rejection is now moot in view of the cancellation of claim 6.

Claim 7 was rejected as indefinite because it is not known how incorporating the recited genes into a gene construct can increase the copy number of the recited genes. This rejection is now moot in view of the cancellation of claim 7.

Claim 10 was rejected as indefinite because the specific enzyme claimed is not known and not recited and the meaning of the word "weakened" is not known. This rejection is now moot in view of the cancellation of claim 10.

Claims 11-13 were rejected as indefinite because the specific genetic modification which results in a "weakened" enzyme is not known and not recited. This rejection is now moot in view of the cancellation of claims 11-13.

Claim 14 was rejected as indefinite because the specific enzyme claimed is not known and not recited and the meaning of the word "weakened" is not known. Claim 14 has been amended to state that the one or more enzymes specifically involved in the synthesis of D-pantothenate are selected from the group consisting of panB, panC, panE and panD and that the activity of the one or more enzymes is reduced or eliminated as a result of deletion of all or a part of the nucleotide sequence encoding said enzyme in the microorganism.

Claims 15 and 16 were rejected as indefinite because the specific genetic modification which results in a "weakened" enzyme is not known and not recited. Claims 15 and 16 have been amended to state that the activity of the enzyme ketopantoate hydroxymethyl transferase (panB), the enzyme pantothenate ligase (panC) or both panB and panC is reduced or eliminated by deletion of all or a part of the nucleotide sequence encoding said enzyme in the microorganism. Similarly, claim 16 has been amended to state that the activity of the enzyme threonine dehydratase (ilvA) is reduced or eliminated by deletion of all or a part of the nucleotide sequence encoding said ilvA in the microorganism.

Claim 17 was rejected as indefinite because the meaning of the phrase "characterized by Corynebacterium glutamicum" is not known. Claim 17 has been amended to state that the microorganism is *Corynebacterium glutamicum*.

In view of the above, withdrawal of this section 112, second paragraph rejection is requested.

At pages 4 and 5 of the Office Action, the Examiner rejected claims 1-4, 6-12, 14, 16 and 17 under 35 USC 102(b) as being anticipated by Reuter, "Genetic and physiological analysis of the formation of pantothenate and valine in Corynebacterium glutamicum", Berichte des Forschingszentrums Juelich (1998) Juel-3606, pages 1-115. The Examiner stated that Reuter teach overexpression of ilvBNCD in combination with a deletion of the ilvA in a microorganism, culturing of the microorganism and subsequent production and accumulation of valine.

Applicants traverse this rejection. The Reuter reference does not qualify as prior art with respect to the present application and cannot be used as the basis for rejecting the claims under section 102(b). Reuter became publicly available after February 26, 1999

as indicated in the letter, submitted herewith as Exhibit A, a translation of which is also submitted, from A. Otto of Forschungszentrum Julich GmbH to Dr. Ute Kratscher which states that Juel-3606, the Reuter reference, was published after February 26, 1999. The present application claims priority from German application DE 199 07 576.0 filed February 22, 1999. The priority date of the present application is before the publication date of Reuter; hence, Reuter is not prior art with respect to the present application. Withdrawal of this section 102(b) rejection is requested.

At page 5 of the Office Action, claims 1,4,6, and 7-9 were rejected under 35 USC 102(b) as anticipated by Inui et al. (JP08089249). The Examiner stated that Inui et al. teach the gene for ilvD, cloning the gene into an expression vector for transforming coryneform bacteria, and using the transformed coryneform bacteria for manufacturing valine and isoleucine.

Applicants traverse this rejection. Claims 1, 4, 6 and 7-9 have been canceled without prejudice and replaced with new claims 18, 19, 29-32 and 40. New claims 18, 19 and 29 are directed to a method for the production of L-valine that employs a micro-organism transformed with a nucleotide sequence encoding ilvD and a nucleotide sequence encoding ilvBNC. New claims 30-32 and 40 are directed to a method for the production of L-valine that employs a microorganism in which the activity of ilvD is increased as a result of mutation of the endogenous gene encoding ilvD. Inui et al. does not disclose the claimed methods for producing L-valine and thus does not anticipate the claimed methods. Withdrawal of this section 102(b) rejection is requested.

At page 5 of the Office Action, the Examiner rejected claims 4, 6, and 7-9 under 35 USC 102(b) as being anticipated by Sato et al. (EP 356739). The Examiner stated that Sato et al. teach the gene for ilvBN, cloning the gene into an expression vector used for transforming coryneform bacteria for manufacturing valine, isoleucine, or leucine.

Applicants traverse this rejection. Claims 4, 6, and 7-9 have been canceled without prejudice and replaced with new claims 18, 19, 29, 32 and 40. As discussed above, new claims 18, 19 and 29 are directed to a method for the production of L-valine that employs a microorganism transformed with a nucleotide sequence encoding ilvD and a nucleotide sequence encoding ilvBNC. New claims 32 and 40 depend from new claim 30, which is directed to a method for the production of L-valine that employs a

microorganism in which the activity of ilvD is increased as a result of mutation of the endogenous gene encoding ilvD. Sato et al. does not disclose a method for producing valine that employs a microorganism is transformed with a nucleotide sequence encoding ilvD or a microorganism in which the activity of ilvD is increased as a result of mutation of the endogenous gene encoding ilvD. Sato et al. does not anticipate the claimed methods of producing L-valine. Withdrawal of this section 102(b) rejection is requested.

In view of the above, the present application is believed to be in a condition ready for allowance. Reconsideration of the application is requested and an early Notice of Allowance is earnestly solicited.

Respectfully submitted,
CONNOLLY BOVE LODGE & HUTZ LLP

Date: September 7, 2004

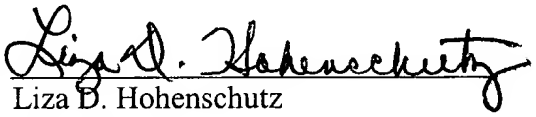
By: 
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EXHIBIT A

Exhibit A Serial No. 09/914,006

Forschungszentrum Jülich GmbH

HAUSMITTEILUNG

A. Otto, ZB

Kopie: Frau Plott/ZB

Vae	Fachbereich Patente R - P	Eg
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An
Frau Dr. Ute Katscher

R-P

Ihre Nachricht vom/Zeichen	Bei Beantwortung bitte angeben	Telefon	Telefax	Datum
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Veröffentlichung: JÜL-Bericht JÜL-3606 von Dr. U. Reuter, Diss. an der Universität Düsseldorf

Sehr geehrte Frau Dr. Katscher,

ich nehme Bezug auf Ihre Anfrage bei Frau Plott zum Veröffentlichungszeitpunkt des Jül-Berichtes JÜL-3606. Aus unseren Unterlagen geht folgendes hervor:

- das Manuskript der Schrift mit dem Titel „"Genetische und physiologische Untersuchungen zur Panthothenat- und Valinbildung in Corynebakterium glutamicum" von Herrn Uwe Reuter wurde am 15.06.1998 gemäß Veröffentlichungsrichtlinien im FZJ zur Drucklegung freigegeben,
- über unseren Eigenverlag wurde daraufhin die Schrift als Auftrag an die Druckerei weitergegeben, am 6.07.1998 als JÜL-Bericht 3552,
- per Anruf vom 14.08.1998 hat Herr Reuter die Drucklegung stoppen lassen, mit dem Hinweis, es werde ein Patent eingereicht,
- der Auftrag wurde in der Druckerei gestoppt, die JÜL-Nummer gestrichen,
- Frau Förstel/IBT teilte am 2.12.1998 mit, dass die Drucklegung jetzt erfolgen könne, da die Patentangelegenheit erledigt sei,
- die Freigabe an die Druckerei für die Drucklegung der o.a. Schrift wurde am 3.12.1998 erteilt, die Schrift erhielt eine neue JÜL-Nummer, JÜL-3606,
- **am 26.02.1999 wurden die gedruckten Exemplare an die Zentralbibliothek geliefert,**
- **nach dem 26.02.1999 wurde der JÜL-Bericht JÜL-3606 an Tauschpartner versendet und damit der Öffentlichkeit verfügbar gemacht.**

Diese Details sind den Unterlagen zu diesem Vorgang zu entnehmen, die ich Ihnen gerne mit diesem Schreiben in Kopie beilege.

Mit freundlichen Grüssen,

A. Otto

- Anlagen: Kopie Begleitformular für Veröffentlichung JÜL-3552 bzw. JÜL-3606,
Kopie Karteikarte zur Verwaltung der JÜL-Schriften für JÜL-3606